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N-Heterocyclic Carbene-Catalyzed Generation of Homoenolates: γ-Butyrolactones by Direct Annulations of Enals and Aldehydes

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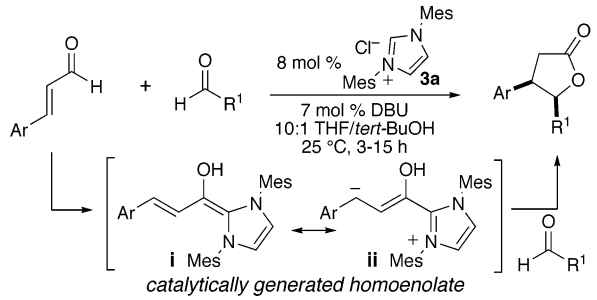
The discovery of new catalytic methods for carbon−carbon bond formation remains a formidable challenge in the continuing development of efficient, sustainable chemical processes. In addition to benefits including operational simplicity and atom-economy, such reactions serve as ideal platforms for the evolution of new stereo- and enantioselective methods. These advantages are apparent in recent, remarkable innovations in direct methods for the formation of enolates and their equivalents under remarkably mild conditions.[1] To date, however, no approaches have been reported for the direct, substoichiometric generation of homoenolates, an attractive class of nucleophiles for which there are but few methods of preparation.[2,3] To address this deficiency, we now document the catalytic generation of homoenolates from α,β-unsaturated aldehydes and their application to the stereoselective synthesis of γ-butyrolactones (Scheme 1).

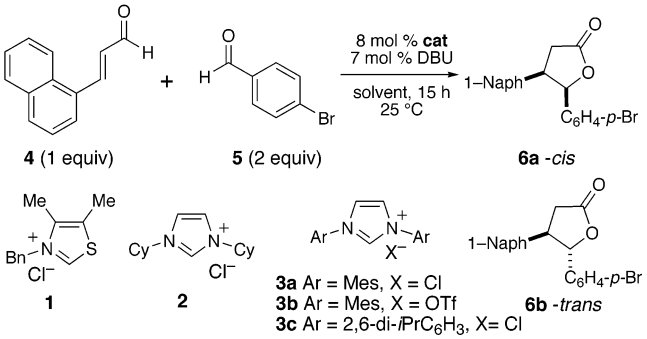
Scheme 1



This novel carbon−carbon bond-forming process is predicated upon our recent discovery of the thiazolium ylide-catalyzed generation of activated carboxylates via intramolecular redox reactions of α-heteroatomic aldehydes.[4] These findings anticipate a similar process from α,β-unsaturated aldehydes via the intermediacy of conjugated acyl anion equivalent **i**. Although **i** would typically be expected to undergo benzoin or Stetter reactions, we reasoned that an appropriate, highly hindered catalyst could (1) shepherd reactivity to the β-position; (2) preclude reactions from the acyl position; and (3) deter protonation events that would quench the incipient homoenolate. Importantly, electrophilic trapping of homoenolate **ii**, followed by tautomerization, would lead to the formation of a catalyst-bound activated carboxylate, which must be displaced to effect catalyst turnover. With these two critical, discrete reaction events in mind, we chose to focus on aldehydes as the electrophilic partner. Coupling of the aldehyde with the homoenolate would lead to an alkoxide poised for intramolecular trapping of the activated carboxylate, affording lactones. This selection, however, was not without potential consequences, as the combination of an enal, an aldehyde, an amine base, and a nucleophilic catalyst presents many competing reaction pathways.

For reaction development we investigated the direct, catalytic annulation of cinnamaldehyde derivative **4** and *para*-bromobenzaldehyde (**5**). As expected, thiazolium catalyst **1** provided none of the desired lactone; only trace amounts of undesired benzoin products were observed (Table 1, entry 1). While bisalkyl imidazolium salts proved to be unreactive (entry 2), the N-heterocyclic carbenes generated in situ from bisarylimidazolium salts exhibited high catalytic activity toward lactone formation (entries 3−5).[5] Interestingly, the stereochemical outcome of the reaction was influenced by catalyst choice (entries 5−7) and formation of the cis isomer was favored.[6] The reaction proceeded in a variety of solvents (entries 7−11), including THF/water mixtures (entry 10). We have found lactone formation to be slightly facilitated by the presence of *t*-BuOH (entry 11) and chose 10:1 THF/*t*-BuOH for further explorations.

Table 1. Development of Catalytic Enal−Aldehyde Annulations[a]



entry	solvent	catalyst	dr **6** (cis:trans)[b]	yield[c] **6a** + **6b** (%)
1	THF	**1**		
2	THF	**2**		
3	THF	**3a**	8:1	74
4	THF	**3b**	8:1	68
5	THF	**3c**	3:2	55
6[d]	THF	**3a**	7:1	68
7[e]	THF	**3a**	8:1	76
8	^{i}PrOH	**3a**	5:1	47
9	EtOAc	**3a**	5:1	64
10	10:1 THF/H_2O	**3a**	7:1	64
11[f]	10:1 THF/*t*-BuOH	**3a**	7:1	84

[a] Unless otherwise indicated, all reactions were performed on a 0.2 mmol scale at 0.5 M for 15 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Mes = 2,4,6-trimethylphenyl; Cy = cyclohexyl. [b] Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [c] Isolated yield following chromatography. [d] Performed with 1.5 equiv **5**. [e] Reaction time 3 h. [f] Performed on a 1 mmol scale; similar results were obtained on a 0.2 mmol scale.

A variety of enals with extended conjugation serve as efficient nucleophiles in direct annulations (Table 2).[7] At the current stage of development the electrophilic reaction partner is limited to aromatic or α,β-unsaturated aldehydes; aliphatic aldehydes do not participate. Although slow addition of the enal provided some advantages, particularly when the highly reactive ynenal was employed (entry 5), in general good yields were obtained simply by mixing the reaction components at room temperature. Lactone dimers of the starting enal, along with small amounts of homoben-

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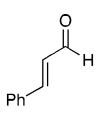
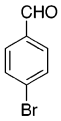
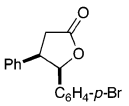
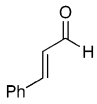
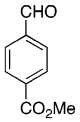
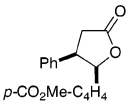
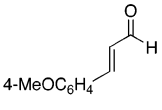
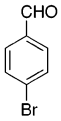
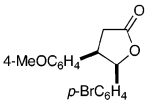
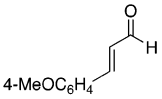
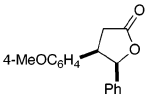
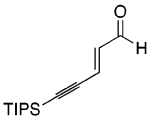
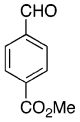
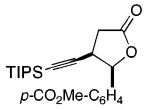
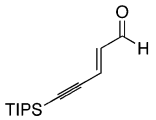
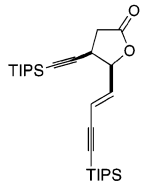
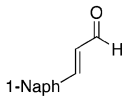
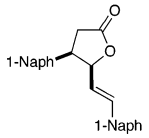
Table 2. Direct, Catalytic Annulations of Aldehydes and Enals[a]

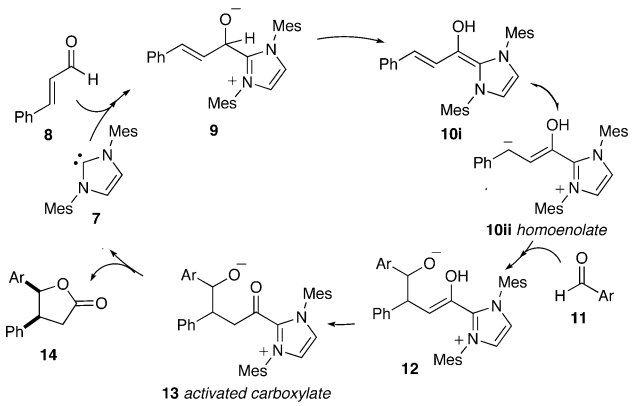
entry	enal	RCHO	product	dr[b]	yield / %[c]
1				4:1	79
2[d]				5:1	87
3				4:1	76
4[e]				4:1	65
5[d,f]				3:1	41
6				5:1	83
7[e]				5:1	67

[a] Reaction conditions: 1.0 mmol enal, 0.5 M in 10:1 THF/*tert*-BuOH at 25 °C for 15 h, 8 mol % **3a**, 7 mol % DBU, 2 equiv of the electrophilic aldehyde. [b] Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [c] Combined yield of both diastereomers after chromatography. [d] Concentration = 0.1 M. [e] Performed with 15 mol % **3a**, 14 mol % DBU. [f] The enal was added over 3 h.

zoin products of the excess electrophilic aldehyde, represent the major byproducts. This process is therefore amenable to the catalytic dimerization of enals, giving good yields of lactones suitable for further functionalization (entries 6 and 7).

Several experiments support the postulated catalytic cycle shown in Scheme 2. The use of *cis*-**4** as a substrate gave an identical stereochemical outcome, rendering the direct addition of **10i** to the aldehyde unlikely. Stopping the reaction prior to completion revealed extensive isomerization to *trans*-**4**, implicating homoenolate **10ii** in the isomerization. Catalytic annulations in the presence of *tert*-BuOD proceeded with stereoselective deuterium incorporation at the α-position of the lactone, indicating that tautomerization to the activated carboxylate occurs after addition of the homoenolate to the aldehyde.[8] The lack of any observed deuterium incorporation at the β-position suggests that despite the protic conditions, quenching of the catalytically generated homoenolate by solvent is neither a major competing pathway nor one that occurs reversibly. While surprising, the finding that protic solvents are not detrimental is consistent with homoenolates stoichiometrically generated from α,β-unsaturated esters under single-electron transfer conditions.[9]

Scheme 2. Postulated Catalytic Cycle for Lactone Formation



In summary, we have documented a catalytic, stereoselective synthesis of disubstituted γ-butyrolactones via the direct annulation of enals and aldehydes. In addition to the synthetic utility of the resulting products, these studies disclose a versatile mechanistic platform for the development of novel carbon−carbon bond-forming processes through the intermediacy of catalytically generated homoenolates and activated carboxylates. The use of an inexpensive, readily available organic catalyst primes this process for further innovations in reaction scope and the development of enantioselective variants.

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Note Added in Proof. During review of our manuscript, we learned of a similar report in press: Burstein, C.; Glorius, F. *Angew. Chem.* In press.

Supporting Information Available: Experimental procedures and characterization data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178. (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368. (c) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (d) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798−6799.

(2) For reviews of homoenolate chemistry, see: (a) Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B., Flemming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 441−454. (b) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932−948.

(3) (a) From silyloxycyclopropanes: Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056−8066. (b) From alkenyl carbamates: Seppi, M.; Kalkofen, R.; Reupohl, J.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 1423−1427. (c) From β-halocarbonyls: Tamaru, Y.; Ochiai, H., Nakamura, T.; Tsubaki, K.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *45*, 5559−5562. (d) From α,β-unsaturated carbonyls: Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *47*, 5763−5764. (e) From β-silyl esters: DiMauro, E.; Fry, A. J. *Tetrahedron Lett.* **1999**, *40*, 7945−7949.

(4) (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126−8127. (b) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518−9519.

(5) For reviews of *N*-heterocyclic carbenes, see: (a) Arduengo, A. J.; Krafczky, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523−14534. (b) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971−985. (c) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130−5135. .

(6) Stereochemistries were assigned by ^{1}H NMR NOE studies and correlation to related products of known configuration; see: (a) Barba, F.; de la Fuente, J. L.; Galakhov, M. *Tetrahedron* **1997**, *53*, 5831−5838. (b) Fukuzawa, S.-i.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482−1483.

(7) Crotonaldehyde, 4,4-dimethyl-pent-2-enal, and α-methylcinnamaldehyde were unreactive under these conditions.

(8) See Supporting Information for details.

(9) We have observed protonation at the β-position, including deuterium incorporation, under more forcing conditions.

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